REMARKS/ARGUMENTS

This amendment is filed in response to the Office Action mailed June 2, 2009 and the Advisory Action mailed September 22, 2009 for the above captioned application. Reconsideration of the application as amended in view of the remarks herein is respectfully requested.

Applicants thank the examiner for taking the time to discuss this application with their attorney in order to move it forward to a condition for allowance. This paper will serve as Applicants summary of the interview.

Amendments Addressing Art Rejections

As discussed, claim 121 has been divided into two independent claims relating to the two types of "binding partners" previously referred to: amended claim 121 which now refers to monoclonal antibodies and fragments, and new claim 204, which refers to recombinant antibodies. Claims 205 to 213 are added dependent on new claim 204 with the same language (except for conforming to the preamble) as in prior claims 126, 127, 129, 130, and 133-137 which are dependent on claim 121.

Claim 122 has been canceled since it is a duplicate of amended claim 121, and non-elected claims 176-178, 187-188 and 193-194 have been canceled without prejudice to the filing of a divisional. As discussed below, claim 203 has also been canceled, so that there is no increase in the total number of claims.

As amended, claim 121 recites human monoclonal antibodies or fragments thereof, that have two characteristics: inhibition of TSH binding to the TSH receptor and stimulation of cAMP production by cells expressing the TSH receptor. As suggested by the Examiner the statement of these characteristics has been made more explicit. This amendment is believed to overcome the anticipation rejection over WO 91/09137 since this reference does not disclose monoclonal antibodies, but only polyclonal mixtures.

As discussed at the interview, this amendment also overcomes the rejection under § 103, because none of the antibodies described in the secondary references exhibit both inhibition of TSH binding and stimulation of cAMP production as recited in claim 121.

House-keeping amendments have been made to claims126, 127, 129, 130, and 133-137 and 199in view of the change to the preamble of claim 121.

As discussed at the interview, Claim 202 has been amended to include the limitations of claim 203. This amendment is believed to overcome the rejection of the claim under § 102 as claim 203 was not rejected.

Provisional Obviousness-Type Double Patenting

As discussed at the interview, no terminal disclaimer should be necessary in this case because this application should place this application in form for allowance, and the cited application was filed after this application and has not yet issued.

Withdrawn Claims

Consistent with the discussion at the interview, Applicant has not canceled the withdrawn claims but authorizes the Examiner to do so if, after reconsideration, she cannot properly recombine the claims. In particular it is understood that the examiner will not recombine the claims if the search as conducted for the examined claims would not reasonably have located art for the withdrawn claims, or if the withdrawn claims raise separate issues of enablement or written description,

For the Examiner's convenience, it is noted that the withdrawn claims can be grouped as follows:

(1) Claims 162 and claims 157-159 and claims 163-167 dependent thereon, which relate to a method for making a human monoclonal antibody with the characteristics recited in the examined claims.

(2) Claims 168-171 which relates to a method for screening for autoantibodies to TSH in a sample using a binding partner which may be a monoclonal antibody as in claim 121 or a recombinant antibody as in claim 204. In anticipation that this use might be recombined in this application, Claim 168 has been amended to conform to the language of these two claims.

(3) Claims 173 which relates to a method for assaying for TSH or related ligands using a binding partner which may be a monoclonal antibody as in claim 121 or a recombinant antibody as in claim 204. In anticipation that this use might be recombined in this application, Claim 173 has been amended to conform to the language of these two claims.

(4) Claim 174 which relates to a method for evaluating a potential binding partner for the TSH receptor using a binding partner which may be a monoclonal antibody as in claim 121 or

a recombinant antibody as in claim 204. In anticipation that this use might be recombined in this application, Claim 174 has been amended to conform to the language of these two claims.

(5) Claim 175 which relates to a method for identifying epitopes of TSH recptor using a binding partner which may be a monoclonal antibody as in claim 121 or a recombinant antibody as in claim 204. In anticipation that this use might be recombined in this application, Claim 175 has been amended to conform to the language of these two claims.

Applicants note that the methods of claims 168-171 and 173-175 are very similar in method steps and all rely on the binding specificity of antibodies of the invention. Thus, Applicants submit that they are reasonably kept together with the base composition claims.

(6) The remaining withdrawn claims relate to methods of treatment or therapeutic combinations. During the interview the Examiner indicated that it was likely that these would be considered to raise additional issues such that they would not be recombined. If recombination is appropriate, however, Applicants will agree to an Examiner's amendment or submit a further supplemental amendment to make the same type of amendment as in the claims discussed above.

Information Disclosure Statement

As mentioned during a supplemental interview on October 9, 2009, Applicants have identified three references which were cited in corresponding foreign application which were inadvertently not previously disclosed in this case. An IDS form listing these references, with copies of the references is filed herewith. Applicants do not believe that these references should delay allowance of this application, but request that the Examiner advise so that Applicants may promptly file an RCE if this is required to have the references considered.

The three references were cited as additional references in the first office action issued by the European Patent Office. For the Examiner's convenience, copies of all three European Office Actions issued to date are attached. It is noted, however, that the claims in the European application are broader than those now pending in this application, and do not contain the limitations to both functional characteristics.

(1) Akamizu et al 1996: Molecular analysis of stimulatory anti-thyrotropin receptor antibodies (TSAbs) involved in Graves' Diseases, Journal of Immunology 157: 3148 – 3152

This document describes the isolation of the monoclonal antibodies mentioned in the Akimazu et al (1999) paper: these two papers are related. Accordingly, the arguments previously put to the examiner regarding the 1999 paper also apply to this reference. In particular, we note that these antibodies do not inhibit the binding of TSH to the TSH receptor (this is shown in table 111 of this paper), and therefore the antibodies described by Akimazu do not have the two functional characteristics required by our claims – whilst there is some indication that they stimulate cAMP production by cells expressing the TSH receptor, it is explicitly taught that they do not have the first characteristic set in the claims (i.e. inhibiting TSH binding to the TSH receptor.

(2) Yoshida et al 1988: Monoclonal antibodies to the thyrotropin receptor bind to 1 56-kDa subunit of the thyrotropin receptor and show heterogenous activities JBC 263(31): 16341 – 16347

This document relates to antibodies to the TSH receptor. The disclosure of Yoshida is similar to that of the Valente document previously cited in the US, in that it purports to disclose monoclonal antibodies having the characteristics of patient serum autoantibodies to TSH (and in particular the characteristics set out in claim 121). However, as for the Valente document, this disclosure of human monoclonal antibodies which are purported to have the characteristics of patient serum TSH receptor autoantibodies is suspect, and this has been recognised in subsequent papers, including the papers already submitted to the US examiner in connection with Valente. For example, Ando and Davies (Clinical and Developmental Immunology 12(2): 137 - 143) note that the antibodies reported in the Yoshida paper (among others) "showed stimulating or blocking activity only at high concentrations ... these mAbs did not show any TSH competing activity ... no clinical significance could be assigned to them" (Page 139, first column). Similarly, Rappaport et al (Endocrine Reviews 19(6): 673 to 716) report significant concerns over the prior art reports of monoclonal antibodies to TSHR (page 698, second column). They state that they "remain uncertain of the specificity of the human TSHR mAbs generated, none of which presently meet all of the criteria [set out by Rappaport for confirming the cloning of disease associated human TSHR auroantibodies]". Rappaport goes on to comment specifically on this paper (reference 246), and throws doubt on the claims made. Rappaport is of the view that the results in this and other papers "should be viewed with caution". In particular, it is stated that

"the specificity of these mAbs is open to question. Thus, functional effects were observed at extremely high mAb concentrations and interaction with the TSHR was tested by competition with 10-6 M TSH. Moreover, immunoblots with these antibodies are inconsistent with the presently known structure of the TSHR."

Therefore, Applicants submit that it would be clear to the skilled person, aware of the art as a whole, that although Yoshida et al claim to have isolated monoclonal antibodies having certain desirable characteristics, these claims are unsupported – the subsequent doubts thrown on this paper indicate that such monoclonal antibodies were not, in fact, obtained.

(3) Bulow Pedersen 2001: TSH-receptor antibody measurement for differentiation of hyperthyroidism into Graves' disease and multinodular toxin goiter: a comparison of two competitive binding assays Clinical Endocrinology 55: 381 – 390

This reference is cited in Europe, but is not relied upon by the examiner in connection with novelty or inventive step of the claims to the monoclonal and recombinant antibodies of the invention. This document is mentioned only in connection with standard assays for determining the binding of TSHR antibodies to the TSH receptor, based on competition with TSH. This document is concerned with diagnostic tests for discriminating between Graves' disease and multinodular toxic goitre, and although patient autoantibodies are discussed, no human monoclonal or recombinant antibodies are disclosed.

For the foregoing reasons, Applicants submit that this application is now in form for allowance. Should there be minor matters which might be resolved by telephone to achieve allowance, the Examiner is encouraged to call the undersigned.

Respectfully submitted,

Marina T. Larson

Marina T. Larson, Ph.D
Attorney/Agent for Applicant(s)
Reg. No. 32038

(970) 262-1800

EP: 1 of 4.

Europäisches Patentamt | European Patent Office | Office européen des brevets

Generaldirektion 2 | Directorate General 2 | Direction Générale 2

Telephone numbers:

Primary Examiner (substantive examination) +49 89 2399-7710

Formalities Officer / Assistant (Formalities and other matters) +49 89 2399-0

LLP
Alexandra House,
1 Alexandra Road
Swansea SA1 5ED
ROYAUME-UNI

RECEIVED
25 MAY 2006
URQUHART DYKES & LORD LLP
SWANSEA

Application No.	Ref.	Date
03 778 537.5 - 2402	VJS/P452347EP	22.05.2006
Applicant: RSR LIMITED		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application bei withdrawn (Article 96(3) EPC).

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OFFICE DIARY 22/9/06
COMMS

Ulbrecht, M
Primary Examiner
for the Examining Division

30/06.

Enclosure(s): 8 page/s reasons (Form 2906)
Kohn 1997.; Akamizu 1999, 1996; Yoshida 1982; Pedersen 2001
WO 99/64865, WO 2004/048415

Registered Letter
EPO Form 2001 07.02CSX

The examination is being carried out on the **following application documents:**

Description, Pages

1-107 as published

Sequence listings part of the description, Pages

1-10 as published

Sequence listings, Pages

1-10* filed with entry into the regional phase before the EPO

Claims, Numbers

1-98 filed with entry into the regional phase before the EPO

Drawings, Sheets

1/16-16/16 as published

Comments

* to be published as annex.

1. *Cited documents:*

cited in ISR

D1: WO 91/09137 A (RAPOPORT) 27 June 1991 (1991-06-27)

D2: KOHN, L.D. ET AL.: Characterization of monoclonal thyroid-stimulating and thyrotropin binding-inhibiting autoantibodies from a Hashimoto's patient whose children had intrauterine and neonatal thyroid disease' JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM 82(12):3998-4009 (1997)

D3: AKAMIZU, T. ET AL.: 'Characterization of recombinant monoclonal antithyrotropin receptor antibodies (TSHRAbs) derived from lymphocytes of patients with Graves' disease: epitope and binding study of two stimulatory TSHRAbs' ENDOCRINOLOGY 140(4):1594-1601 (1999)

D4: AKAMIZU, T. ET AL.: 'Molecular analysis of stimulatory anti-thyrotropin receptor antibodies (TSAbs) involved in Graves' disease' JOURNAL OF IMMUNOLOGY 157:3148-3152 (1996)

D5: YOSHIDA, T. ET AL.: 'Monoclonal antibodies to the thyrotropin receptor bind to a 56-kDa subunit of the thyrotropin receptor and show heterogeneous bioactivities' THE JOURNAL OF BIOLOGICAL CHEMISTRY 263(31):16341-16347 (1998)

D6: VALENTE, W.A: ET AL.: 'Monoclonal antibodies to the thyrotropin receptor: Stimulating and blocking antibodies derived from the lymphocytes of patients with Graves disease' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES U.S.A. 79:6680-6684 (1982)

D7: BÜLOW PEDERSEN, I. ET AL.: 'TSH-receptor antibody measurement for differentiation of hyperthyroidism into Graves' disease and multinodular toxic goitre: a comparison of two competitive binding assay' CLINICAL ENDOCRINOLOGY 55:381-390 (2001)

D8: WO 99/64865 (RSR LTD.) 16 December 1999 (12-16-1999)

D2-D8 have not been cited in the ISR but are introduced into the procedure in accordance with Gl. C-VI 8.7. A copy of said documents is annexed to the present communication.

2. *Amendments (Art. 123(2) EPC):*

The amendments as filed with form 1200 do not appear to introduce subject-matter beyond the original disclosure of the application and thus meet the requirements of Art. 123(2) EPC.

3. *Clarity (Art. 84 EPC):*

3.1 Claims 10-21, 32-37, 47-56, 61-68 define their subject-matter using a parameter, namely by reference to the units of a specific international standard. The clarity of said parameter depends on the availability of the said standard which appears not to bo guaranteed throughout the life time of a patent possibly granted on the said subject-matter. Hence, said claims are objectionable on grounds of clarity under Gl. C-III 4.7a. Furthermore, said parameters appear, at least insofar as claims 10-21, 47-55, 63, 64, 67 and 68 are concerned to disguise lack of novelty (cf. 4.2, 4.3 and 4.5). Finally, these parameters as used in said claims amount to a definition of the claimed subject-matter in terms of a result to be achieved objectionable also under Gl. C-III, 4.7. The technical features required to achieve these activities/ sensitivities are not determinable. Said claims thus lack clarity.

3.2 Claim 84 refers to an anti-idiotypic antibody defined by its generic name which is not sufficient to clearly define the subject-matter of said claim. Although the reference to the examples as providing the method according to which said antibody is prepared does not inevitably lead to i.e. define said specific antibody. Therefore, said antibody also appears not to be disclosed in a way sufficiently disclosed for the skilled person to perform this feature of the invention (Art. 83 EPC).

3.3 Claims 1-6, 22-25, 28, 38-40, 60-69 and 71-76 have been drafted as separate independent claims.

Under Art. 84 in combination with R. 29(2) EPC an application may contain more than one independent claim in a particular category only if the subject matter claimed falls within one or more of the exceptional situations set out in paragraphs (a), (b) or (c) of R. 29(2) EPC. This is not the case in the present application however, for the following reasons:

- claims 1-6, 22-25, 28 and 38-40 all refer to binding partners for the TSH receptor and could be made dependent on each other;

- claims 60-64 and 69 all refer to methods of screening for TSH receptor antibodies and could be made, at least in part, dependent on each other; the same applies to the corresponding kits for performing said method as suggested by claims 71-76;

- claims 65-68 refers to uses corresponding to the screening methods of claims 60-64 and 69 and could equally be made, at least in part, dependent on each other.

In the further prosecution of the application, failure to file an amended set of claims which complies with R. 29(2) EPC, or to submit convincing arguments as to why the current set of claims does in fact comply with these provisions, may lead to refusal of the application under Art. 97(1) EPC.

4. *Exclusions from patentability (Art. 52(4) EPC):*

Claims 47-56, 60-64, 69 and 78 comprise a step of "providing a sample of a body fluid from a subjec"t which embraces the actual step of obtaining said body fluid by a sampling step considered surgical, thereby rendering the entire method/process a surgical method/process which is not susceptible to industrial applicability and thus excluded from patentability. This objection can be overcome by introducing the disclsimer "in vitro method/process".

5. *Novelty (Art. 54(3) and (4) EPC):*

The PCT application WO 2004/048415 (D8) published on 10.06.2004 claims the priority date of 26.11.2002 It has been supplied to the European Patent Office in one of its official languages and the national fee provided for in Art. 22, paragraph 1 or Art. 39, paragraph 1 of the Co-operation Treaty has been paid. The requirements of Art. 158(2) EPC are thus fulfilled.

Its content as filed is therefore considered as comprised in the state of the art relevant to the question of novelty, pursuant to Art. 54(3) and (4) EPC. This earlier application shows:

A competitive binding assay for the detection of TSHR autoantibody using purified polyclonal human TSHR autoantibodies as competitors and comprising the steps of present claims 62 and 70; as well as a kit comprising the components according to claim 73, wherein the sensitivity of the reagents used is considered to inherently fall under that suggested by any of said claims (cf whole of D8).

Thus, it is prejudicial to the novelty of the subject-matter of claims 62, 66, 70 and 73 of the present application insofar as the same Contracting States AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR are designated.

The following examinations assumes that the foregoing novelty objections have successfully been overcome.

6. *Novelty (Art. 54(1) and (2) EPC):*

6.1 D2 teaches human monoclonal antibodies (mAbs) binding to the TSH receptor (TSHR) that either inhibit TSH binding or stimulate a cAMP response (abstract). These antibodies are produced by heterohybridoma technology using PBLs from a patient suffering from Hashimoto's thyroiditis (p. 3999, c. 1, para. 3 - p. 4001, c. 2, para. 1). Some of the nonstimulatory mAbs also blocked the binding of a stimulatory Graves' disease IgG preparation (Tab. 4; Fig. 5). D2 is thus prejudicial to the novelty of claims 1, 2, and 4.

D3 teaches the epitope mapping of two human recombinant thyroid-stimulating TSHR mAbs derived from EBV-immortalised lymphocytes of patients with Graves disease (abstract; p. 1595, c. 1, para. 3 - p. 1596, c. 2, para. 2). The method of isolating and recombinantly expressing the said antibodies is disclosed in D4 which also includes a teaching of the vectors and transfected myeloma cells used therein (abstract; p. 3148, c. 2, para. 4 - p. 3150, c. 1, para. 1) Fig. 1). D3 and D4 therefore destroy the

novelty of claims 1-6 and 57 Furthermore, claim 82 lacks novelty over D3.

D5 teaches the characterisation of human TSHR mAbs isolated from patients with Graves' disease by means of hybridoma technology. Two antibodies inhibit TSH binding and are shown in an cAMP response assay to be either stimulatory or inhibitory. Two further antibodies which do not inhibit TSH binding behave stimulatory and inhibitory, respectively in said cAMP response assay (abstract; p. 16341, c. 2, para. 4 - p. 16344, c. 2, para. 2). Consequently, claims 1, 2 and 4 lack novelty over D5.

D6 discloses human stimulating and blocking TSHR mAbs isolated from Graves' disease patients' lymphocytes by heterohybridoma technology. One such mAb (208F7) blocks binding of TSH and increases cAMP levels (abstract; p. 6680, c. 2, para. 2 - p. 6681, c. 1, para. 4; Fig. 1 and 2). Hence, D6 destroys the novelty of claims 1, 2 and 4.

6.2 The lymphocytes used to obtain the TSHR mAbs of D1-D6 are isolated from individuals whose sera are considered to inherently display the inhibitory/stimulatory activities suggested by claims 47(i) and 48(i) (cf. 3.1). Hence, said documents also destroy the novelty of claims 47 and 48.

6.3 Assays for determining TSHR antibodies based on competition with TSH for binding to the TSHR are known from D1 (Example 8), D2 (p. 4000, c. 2, para. 4), D5 (p. 16342, c. 2, para. 3), D6 (p. 6681, c. 1, para. 2), D7 (whole document) and D8 (whole document). The affinity of TSH to the TSHR is considered to be at least 10^{10} $molar^{-1}$ and the sensitivity of said assays is considered to inherently fulfill the requirements of claims 63, 64, 67 and 68. Hence, the subject-matter of claims 63, 64, 67 and 68 lacks novelty over any of D1, D2 and D5-D8.

6.4 The additional features suggested by claims 7-9 and 70 are disclosed by at least one of D1-D6 (supra). Moreover, the additional features suggested by claim 58 are disclosed in D4 (supra). Hence, claims 7-9, 58 and 70 do not establish novelty.

6.5 Moreover, as the inhibitory/stimulatory activities of the TSHR mAbs/sera

produced/used in D1-D6 are considered to inherently fall within the functional definitions given by any of claims 10-21 and 49-55, these functional features do not establish novelty over D1-D6 where applicable (supra).

7. *Inventive step (Art. 56 EPC):*

7.1 Claims 22-42 suggest alternative TSHR binding partners, namely TSHR antibodies which are arbitrarily selected from equally likely alternatives to any of the antibodies according to D2-D6. These binding partners i.e antibodies as they do not appear to bring about any technical effect not known from D2-D6 and, as their generation only requires routine experimentation largely taught by any of D2-D6 do not establish an inventive step.

7.2 The same considerations also apply to the corresponding polynucleotides encoding said antibodies, as well as to vectors and host cells containing said polynucleotides. Hence, claims 43-46 are not inventive.

7.3 The additional features suggested by claims 56 and 59 are routine modifications of the processes known from any of D2-D6 which do not produce any unforeseeable technical effect, but which are arbitrarily introduced. These claims do not establish an inventive step.

7.4 The concept of competitive binding assays for the detection of specific antigens/ligands is general knowledge and the application thereof for the detection of TSHR autoantibodies in sera is a matter of routine, as exemplified by the disclosures of D1, D2 and D5-D8. Claims 60-62, 65, 66 and 69 are distinguished from any of said disclosures by the use of a different competitor instead of TSH. Human TSHR autoantibodies including the TSHR mAbs falling under any of claims 1-21 are known from the prior art (cf. 6.1, 6.4 and 6.5). Using said autoantibodies mono- or polyclonally would be a routine modification of the standard competitive binding assay for the detection of TSHR Abs which does not produce any unforeseeable technical effect. This modification is arbitrarily selected and does render claims 60-62, 65, 66 and 69 inventive.

7.5 Inclusion of reagents used in a method does not establish an inventive step per se. As the methods according to claim 63 and 64 are not novel (cf. 6.3) and those according to claims 60-62 and 69 are not inventive (cf. 7.4), the corresponding kits according to claims 71-77 do not establish an inventive step.

7.6 Claims 78-81 and 83-98 refer to routine applications of the TSHR mAbs according to any of the D2-D6, immediately derivable from their specificities and functional properties, or to further products (anti-idiotypic antibodies) obtainable by routine experimentation, or to kits for performing the said routine applications. The subject-matter of none of said claims is associated with any unforeseeable technical effect, but relates to arbitrary uses of the known TSHR mAbs. These claims do not establish an inventive step.

6. It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of R. 29(1) EPC. The applicant should also indicate the difference of the subject-matter of the new claim vis-à-vis the state of the art and the significance thereof.

EP: 2nd OA.

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Formalities Officer
Name: Uloreanu, Raluca
Tel: +49 89 2399 - 7713
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Ulbrecht, Matthias
Tel: +49 89 2399 - 7710

A.A. Thornton
235 High Holborn
London WC1V 7LE
ROYAUME-UNI

26717

Application No.	Ref.	Date
03 778 537.5 - 2402	VJS/P452347EP	04.02.2008
Applicant: RSR LIMITED		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Ulbrecht, Matthias
Primary Examiner
for the Examining Division

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Enclosure(s): 6 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents**:

Description, Pages

1-107 as published

Sequence listings part of the description, Pages

1-10 as published

Sequence listings, Pages

1-10 filed with entry into the regional phase before the EPO

Claims, Numbers

1-85 filed with telefax on 18.09.2006

Drawings, Sheets

1/16-16/16 as published

1. *Amendments (Art. 123(2) EPC):*

1.1 Contrary to the requirements of Art. 123(2) EPC the amendments introduce subject-matter beyond the original disclosure of the application. The amendments concerned are the following:

a) Present claim 1 now defines the TSH-R binding partners as having the characteristics of patient serum TSR-R autoantibodies. The only passage in relation to said feature

to be found in the application as filed is at p. 4, last para., 3rd sentence which teaches '*the successful production of a human monoclonal TSH receptor antibody with the characteristics of the autoantibodies found in the sera of patients with hyperthyroid Graves' disease*'. Compared to this passage the underlined features have been omitted or generalised. As these features, however, appear to be essential to the invention they cannot be omitted or generalised without infringing Art. 123(2) EPC (cf. GL. C-VI, 5.3.10).

b) Present claims 18 and 21 now further define the TSH-R binding partners as inhibiting the binding of inter alia TSH receptor autoantibodies. Previously, the antibody was only defined by structural features, the smallest being a VH CDR. These structural are derived from hMAb TSHR1. The binding of this antibody to the TSH-R is taught to be inhibited by TSH-R autoantibody positive sera (p. 71-72) which is at odds with the functional features as suggested now.

The definition of an antibody's specificity in structural terms requires all 6 CDRs and if the antibody's affinity is also only defined structurally, the whole sequences of at least the VH and VL domains are necessary. Previously, the minimum structural requirement of the binding partner was the presence of at least one of the 3 VH CDRs defined by sequence which was not considered to provide any specific property. Therefore, to further define this antibody functional features are required. For claims 18 and 21, the broadest functional definition which appears to be allowable under Art. 123(2) EPC would be a reference to those of present claim 4, as hMAb TSHR1 from which the structural features are derived has the properties defined in claim 4.

1.2 The other amendments appear to have a basis in the application as filed as required by Art. 123(2) EPC.

1.3 The following examination does not take into consideration the features infringing Art. 123(2) EPC.

2. *Disclosure, clarity and conciseness (Art. 83 and 84 EPC):*

2.1 Two parametric definitions are used in present claims 7-17, 28-33, 46-51 and 57. These parameters combine a definition of an assay with a reference to a standard.

One assay relates to inhibitory properties and the other to stimulatory properties. Both parameters use as reference the International Standard NIBSC 90/672. In essence these definitions require that the TSH-R binding partner performs in the indicated assays as least as "good" as the said standard. Previously, doubts as to the availability of said standard has been raised which are waived in view of the applicant's arguments. However, the definitions of the assays are still not considered sufficiently clear to define the claims' subject-matter. The assay is based either on the inhibition of TSH binding to the TSH-R or on the stimulation of cAMP production by cells expressing the TSH-R. The application teaches two specific assays falling under either definition (cf. p. 57, last para. - p. 58, last para.), namely, respectively, a competitive RIA and a cAMP assay using CHO cells expressing approx. 50,000 TSH-R/cell. The definitions of the assays according to the said claims, however, also covers further assays e.g. a cellular TSH-R competition assay or the use of different cells expressing different levels of TSH-R in the cAMP assay which would most likely affect the obtained results, thereby obscuring the claims' scope.

2.2 Furthermore, the said parameters provide an open end definition of the claims' scope by means of the expression "at least". The application teaches a single antibody, namely hMAB TSHR1 having both said properties and a second antibody, namely 9D33 which only has the inhibitory property. Both antibodies were isolated by cloning immortalised PBMC of Graves' disease patients whose sera contained TSH-R autoantibodies. The generation of antibodies having said properties by such a cloning approach is a mere chance event. The disclosed cloning procedure does not comprise any steps which would allow to increase this chance. Hence, the generation of any anti-TSH-R antibodies which have even better inhibitory and/or stimulatory properties is not reproducible as required by Art. 83 EPC.

2.3 Claim 71 refers to a specific antibody, namely 7E51 IgG. The remainder of the claim defines how said antibody was obtained. This latter definition however does not allow to clearly identify the said antibody. The fact that it was generated against a binding region of a binding partner or further binding partner for the TSH-R does not provide any indication of its unique structural and functional properties. Also the method of its preparation taught at p. 66, para. only teaches that it was generated against hMAb TSHR1 and binds thereto. However, this method will not inevitably and reproducibly lead to the generation of a single anti-idiotypic antibody having always the same primary sequence, namely that of 7E51. In fact, the only clear definition of a specific

antibody as referred to in claim 71 is either the provision of its entire amino acid sequence or its deposit according to R. 33 EPC. As neither is available the claimed antibody is not defined (Art. 84 EPC) and lacks reproducibility (Art. 83 EPC).

2.4 Each of claims 39 and 40 appears to suggest a number of alternatives which are however not combined by "or".

2.5 Moreover, claims 39 and 40 refer to an "allelic variation" of any of sequence of (i). This alternative is not combined with a functional limitation. In the context of a polynucleotide encoding a single CDR it is not determinable when a sequence has to be considered an allelic variant as for instance, should the said variation lead to a different CDR, it would belong to a different antibody. Hence, said term does not allow to clearly determine the claims' scope.

2.6 The feature suggested by claim 55 ("is subjected to further processing techniques so as to obtain...") is defined in terms of a result to be achieved. It is not determinable which "further processing techniques" are covered thereby obscuring the claim's scope.

2.7 Claim 64 suggests features which are already present in the antecedent claims it refers to or which are inconsistent therewith. Thus, said claim is either redundant and should be deleted for sake of conciseness or it creates unclarity.

2.8 Claims 77 and 80 refer to agents defined in terms of a result to be achieved ("agents capable of stimulating thyroid tissue" and "agents capable of inactivating or rendering unresponsive..."). It is undeterminable which agents are actually covered by said definitions, thereby obscuring the claims' scope.

2.9 Claims 77-81 use the wordings "in combination" or "a combination according to claim...". It is not determinable whether this wording refers to a composition consisting of the indicated compounds or comprising them.

2.10 In claim 85 the intended use is not limiting the scope of claimed product. Thus said claim is redundant over the claims it refers to and should be deleted for sake of conciseness.

2.11 Pursuant R. 43(2) EPC independent claims 44 and 43 which define specific embodiments of the general method of claim 53 should be made dependent on the latter claim. The same applies for the relation between claims 56 and 59, the latter being a specific embodiment of the subject-matter of claim 56. Likewise, claims 61 and 63 could be made dependent on claim 60.

3. *Novelty (Art. 54(1) and (2) EPC) and inventive step (Art. 56 EPC):*

3.1 For the assessment of novelty and inventive step, the examining division notes the following:

a) D2 and D4-D6 disclose the cloning of autoantibodies specific for the TSH-R from patients suffering either from Graves' disease (D4-D6) or Hashimoto's thyroiditis (D2) and having autoantibodies directed at the TSH-R. The isolated antibodies inherently have the same properties as the patients' sera TSH-R autoantibodies they are derived from. The antibodies are cloned either by heterohybridoma technology (D2, D5 and D6) or following EBV-transformation (D4). The antibodies have both TSH-inhibitory and TSH-R-stimulatory properties as discussed in the previous official communication and the applicant's letter of 18.09.2006.

b) The antibodies of the application were isolated using the same approach. EBV-transformed PBMCs of a Graves' disease patient were used to clone anti-hTSH-R antibodies by heterohybridoma technology. The fact that the PBMCs were EBV-transformed prior to hybridoma formation has no influence on the antibodies' properties. In fact, not even the hybridoma formation affects the antibodies' properties. Formally, the patient used in the present application also suffered from IDDM. However, this additional disease does not have any bearing on the presence of autoantibodies to the TSH-R which is a feature of the Graves' disease. Two antibodies were obtained hMAb TSHR1 and 9D33, the former having both inhibitory and stimulatory properties and the latter only an inhibitory one. As discussed herein above these properties are inextricably linked to the antibodies' specificities. The potency of these properties in turn depends on the antibodies' affinity. The specificity of an antibody is largely dependent on its 6 CDRs, the affinity, however, also requires at least the framework regions of the VH and VL domains.

3.2 Claims 39 and 40 suggest inter alia a "polynucleotide comprising (v) a nucleotide

sequence comprising a fragment of any of the sequences of (i), (ii), (iii) or (iv)". The features following the expression "in particular" are merely optional and do not limit the claims' scope (cf. GL. C-III, 4.9). Consequently, in the absence of any limitation to the length of the fragment or by further functional features and given the open "comprising" claim language any nucleic acid falls under the claims' scope, destroying their novelty.

3.3 The applicant argues that the hMAb TSHR1 has a superior potency over any of the antibodies disclosed in the prior art. This might be the case. However, it is a feature of this very specific antibody defined by at least its whole VH and VL sequences. The claims, though encompassing this antibody, are much broader in scope. For the assessment of novelty, the question to be answered is whether a disclosure of the prior art falls under the scope of said claims. As discussed previously, the examining division considers this to be the case, regardless of whether the hMAb TSHR1 is novel or not. For the analysis of inventive step, the first question to be answered is whether the purported technical effect, namely of an anti-TSH-R antibody having the superior properties of hMAb TSHR1 is achieved over the whole scope of the claims. The examining division denies this, as none of the claims defines an antibody in the required structural terms i.e. by the entire VH and VL sequences of hMAb TSHR1. Thus, at most the proposed antibodies can be regarded as alternatives to the anti-TSH-R antibodies known from any of D2 and D4-D6. As all of these documents disclose methods of isolating such antibodies, the screening for alternatives is a mere question of the skilled person's routine which does not merit an inventive step unless the antibodies indeed have some superior properties i.e. provide a technical effect.

4. Should the above objections not be overcome with the next amendments and in view of a corresponding auxiliary request for oral proceedings already on file, the examining division's next action will be the issuance of summons to oral proceedings.

KP : 2nd OA

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Formalities Officer
Name: Jenney, Helen
Tel: +49 89 2399 - 7713
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Ulbrecht, Matthias
Tel: +49 89 2399 - 7710

Gallafent, Alison
A.A. Thornton & Co.
235 High Holborn
London WC1V 7LE
ROYAUME-UNI

Application No.	Ref.	Date
03 778 537.5 - 2402	~~VJS/P452347EP~~ 2671 7	20.07.2009
Applicant: RSR LIMITED		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Ulbrecht, Matthias
Primary Examiner
For the Examining Division

Enclosure(s): 7 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents**

Description, Pages

1-107 as published

Sequence listings part of the description, Pages

1-10 as published

Claims, Numbers

1-80 received on 05-06-2008 with letter of 28-05-2008

Drawings, Sheets

1/16-16/16 as published

1 *Cited documents:*

D9: Costagliola and Vassart (2002)

D10: Ando et al. (2002)

D11: Sanders et al. (2002)

D12: Ando and Davies (2005)

D13: Rappaport (1998)

D9-D13 have been submitted by the Applicant. The Examining Division (ED) notes that D13 constitutes prior art under Art. 54(2) EPC, whilst D9-D11 would only be relevant under Art. 54 (2) EPC if the the priority date of 29.11.2002 claimed from 0227964.4 were not valid.

2 *Amendments (Art. 123(2) EPC):*

2.1 Contrary to the requirements of Art. 123(2) EPC the following amendments introduce subject-matter beyond the disclosure of the original application:

2.2 Present claim 1 now features that the TSH receptor (TSHR) binding partner has the characteristics of patient serum TSHR autoantibodies found in the serum of patients with hyperthyroid Graves' disease. This feature finds a basis at p. 4, l. 29-31, however only in the context of human monoclonal TSHR antibodies, but not in that of binding fragments comprising or derived from a human monoclonal or recombinant antibody, or one or more fragments thereof. The other passage at. p. 5, last para. defining said broadly defined binding partner by referring to autoantibodies present in patients with Graves' disease is limited to an inhibition of TSH binding to TSHR and/or a stimulation of

TSHR. Moreover, this passage refers to Graves' disease in general covering e.g. also euthyroid disease. Thus, compared to this passage the limitation to hyperthyroid Graves' disease adds subject-matter.

2.3 Present claims 4, 6, 7, 10-13, 16, 17, 28, 29, 32, 33 and 47-49 now specify that the antibodies' inhibitory properties are determined using labelled TSH. The passage at p. 57, l. 22-26 indicated as forming a basis for this feature, however, only refers to ^{125}I-TSH but not to labelled TSH in general. There appears to be no basis for a generalisation from said specific ^{125}I label to any label.

2.4 For newly introduced claim 5 the Applicant failed to give a basis which the ED could also not identify.

2.5 Present claim 18 now depends on claim 4 and features that the binding partner inhibits binding of both TSH and TSHR autoantibodies. Original claim 25 from which present claim 18 is derived did not suggest any functional features, let alone those defined in claim 4. Present claim 18 covers hMAB TSHR1 which as shown e.g. at p. 67, para. 3 displays some of the functional features now proposed by claim 18. However, this antibody is inhibit from binding to TSHR by TSHR autoantibodies whilst the claim requires the opposite i.e. that the claimed antibody inhibits the binding of TSHR autoantibodies (cf. also Item 1.1 (b) para. 1 of the previous official communication dated 04.02.2008). Moreover and contrary to what has been discussed under item 1.1 (b) para. 2 of the previous official communication, even though hMAB TSHR1 inhibits the binding of TSH, this is not a feature inherent to all of the binding partners as structurally defined in original claim 25. Finally, the application does not disclose the feature of inhibiting the binding of TSHR autoantibodies in the context of a generically defined TSH binding partner, let alone of such binding partners further featuring the inhibition of TSH binding.

2.6 The considerations 2.5 under apply *mutatis mutandis* to claim 21 as well as to the resepctive dependent claims 19, 20, 22 and 23.

2.7 Present claim 59 does not specify that the second molecule referred to in claim 56 is a full length TSHR, or one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSHR as derivable from the application as originally filed. In fact, by using an open "comprising" language claim 59 leaves open how its steps are to be combined with those of claim 56 if at all, thereby giving way to originally undisclosed embodiments.

2.8 The considerations under 2.7 apply *mutatis mutandis* to the kit according to claim 63 as dependent on claim 60.

2.9 Not withstanding the deficiencies under Art. 123(2) EPC, the following observations with respect to other criteria of patentability are made to expedite the procedure.

3 *Clarity (Art. 84 EPC):*

3.1 Claims 1, 12 and 14 refer to a binding partner derived from a human or recombinant antibody having functional features as specified. It is not determinable when a binding partner having said properties has to be considered as being derived from a human or recombinant antibody. In fact, this language extents the scope to any antibody having the said functional features.

3.2 Claims 1-4 require the TSHR binding partner to have characteristics of patient serum TSHR autoantibodies found in the serum of patients with hyperthyroid Grave's disease. As discussed at p. 1, para. 3 these antibodies, depending on the patient may be stimulatory as well as inhibitory. Moreover, as derivable from the characteristics of the International Standard NIBSC 60/672 the inhibitory/ stimulatory potency of TSHR autoantibodies contained in patients' serum is also variable. Thus, without a clear definition of the reference serum containing TSHR autoantibodies, both in qualitative and quantitative terms, the scope of claims 1-4 remains indeterminable. For the purpose of examination and as concerns claim 1 any TSHR antibody cloned from a hyperthyroid Graves' disease patient is considered to inherently display the characteristics of said autoantibody. As concerns claims 2-4, any inhibitory and stimulatory antibody, respectively, derived from a hyperthyroid Graves' disease patient regardless of its potency has to be considered to fall under the claims' scope. Moreover, in view of the considerations under 3.1 any TSHR antibody with stimulatory and/or inhibitory properties regardless of its source has to be considered to also have the characteristics of patient serum TSHR autoantibodies found in the serum of patients with hyperthyroid Graves' disease.

3.3 Claim 24-38 refer to a further binding partner. It is unclear to what extent this term is considered to limit the claims' scope.

3.4 Claims 39(v) and 40(v) refer to themselves whereby unclarity is created.

3.5 Claim 54 appears to be redundant over claims 48-53 as it does not propose any further technical features. It should be deleted for sake of conciseness.

3.6 Claims 60, 61, 62, 63, 65 and 67 refer to "means for contacting" and "means for monitoring" an interaction. Whilst the reactions that are supposed to occur are sufficiently clear, the scope of said means remains indeterminable.

3.7 Claims 56, 60, 61, 62, 64, 65 and 66 refer to a "second molecule comprising a binding region with which the first binding molecule interacts". There are further independent and dependent claims which imply that one embodiment of said second molecule is a full length TSHR, or one or more epitopes thereof or a polypeptide comprising one or more epitopes of the TSHR. It is not determinable which other molecules apart from said TSHR are covered by the said term, thereby obscuring the claims' scope.

3.8 Claim 75 defines the further agent of a composition as comprising recombinant human TSH and/or variants, analogs, derivates or fragments thereof. Its dependent claim 76 requires that this further agent acts independently of binding to the TSHR. This property is not consistent with the TSH proposed in claim 75 which inherently interacts with TSHR.

3.9 Claim 80 refers to a use of a TSHR binding partner in a preparation required to comprise a defined concentration of TSHR antibody/antibodies. As the concentration of TSHR antibody/antibodies remains undefined, the preparation is unclear. Moreover, the scope of a use in a preparation as compared to a use of a preparation is indeterminable (emphasis added).

4 *Novelty (Art. 54(1) and (2) EPC):*

4.1 As discussed under 3.2 TSHR antibodies derived from hyperthyroid Grave's disease patients inherently have the characteristics of autoantibodies present in the said patients' sera as they represent a part of the pool of said autoantibodies. Moreover, it is noted as also derivable from the dependency of claims 2 and 3 on claim 1 that it is not a requirement of the binding partner to have both properties, namely of stimulating the TSHR as well as of inhibiting the TSH binding to the TSHR. In fact, the claims also cover binding partners which display only one of said properties. D4-D6 indisputably disclose antibodies isolated from hyperthyroid Graves' disease patients. The Applicant contested that the antibodies of D4-D6 represent TSHR autoantibodies found in the patients' sera. In support of this allegation he cited D9-D13.

4.2 At p. 1039, r-h c. 2nd full sentence D9 comments on the results reported in D6 (here reference 14) in stating that '*[a]fter initial claims for the isolation of human monoclonals with TSAb activity (14,15), it became clear that the biological activity of these was well below what was expected for the high affinity thyroid stimulating autoantibodies of Graves' patients*' (emphasis added). This statement does not invalidate that the cloned antibodies are TSHR antibodies found in sera of Graves' patients. It only points to the fact that these antibodies did not represent the high affinity antibodies also present in the serum. Again it has to be borne in mind that none of claims 1-4 requires any particular affinity or stimulatory/inhibitory potency. The Applicant also referred to a statement further down in the text of D9 which reads '*[t]his led several groups ... to doubt that monoclonal antibodies with TSAb activity would exist at all*'. This statement is linked to the preceding report that the generation of hybridomas from mice with experimentally (by immunisation with TSHR encoding cDNA) induced hybridomas only yielded mAbs with TBII and TSBAb activity. Thus the former statement is a comment on the experimental model and furthermore since claim 1 also covers inhibitory TSHR antibodies and claim 2 is exclusively drawn thereto not applicable to these two claims, as blocking mAbs apparently have been obtained in said animal model.

4.3 In support of his argumentation the Applicant also referred to D10 which states at p. 1668, r-h c. para. 2 that '*[h]owever, these thyroid-stimulating activities were only achieved by high concentrations of IgG and some reports even lacked proof of specific TSHR antigen recognition*'. This statement concerns 5 previously published reports on the isolation of antibodies from Graves' patients including D6 (here citation 14). The second half of said statement asserts that some reports lacked proof of specificity without providing a direct link to D6 (emphasis added). Moreover, as discussed hereinabove the possible low potency of the antibodies obtained, as reflected by the need of high concentrations of IgG to achieve thyroid-stimulating activities, does not establish novelty. Finally, D6 not only refers to stimulating antibodies, but also to inhibitory antibodies also covered by claim 1 and exclusively covered by claim 2.

4.4 As concerns the statement in D11 at p. 1043, l-h c., penultimate sentence that '*we are not aware of any reports of high affinity TSHR MAbs which can act as thyroid stimulators and inhibit TSH binding to the TSHR*' it has to be noted that again this statement only refers to high affinity antibodies, a feature not required by the claims. Moreover, this statement covers a specific subset of antibodies which are inhibitory on TSH binding and stimulatory on TSHR (emphasis added), whilst the claims also cover antibodies having only one of said two properties. This conclusion also applies to the second passage at p. 1047, r-h c., para. 2 implicated by the Applicant that the undoubtedly thyroid stimulating MAbs isolated e.g. in D4 (here reference 36) did not in addition inhibit TSH binding to the TSHR. The subsequent sentence that '*these previously described MAbs did not have the characteristics of TSHR autoantibodies*' is not specifically linked to D4 and moreover appears to refer exclusive to this subset of autoantibodies which are both stimulatory and inhibitory.

4.5 The observations made in relation to D9-D11 equally apply to the Applicant's attack on enablement of the disclosures of D5 and D6 based on the passage at p. 139, l-h c., para. 2 of D12. Neither the question of low potency possibly reflected by the need of high antibody concentrations to achieve a stimulating or inhibiting activity, nor the fact that the antibodies possibly do not display a TSH competing activity is an issue in view of the claims' broad scope.

4.6 As concerns the Applicant's attack based on D13, it is noted that the statement at p. 698, r-h c., para. 1 in relation to D5 (here reference 246) that '*[t]he specificity of some human mAbs tested by immunoblotting (246) is now less certain in the light of new information on TSHR structure*' (emphasis added) only casts doubts on the specificity of some of the antibodies but not all of the antibodies disclosed in D5. Moreover, said statement does not fulfil the standard set by the Boards of Appeal required to unequivocally proof that a prior art document is not enabling (cf. Case Law 5th Ed. 2006, I.C.2.10 para. 6, discussion of T 230/01). At most this statement suggests to retest the antibodies' specificity, but fails to demonstrate that they do not react with TSHR. The same considerations apply to the statement in the next para. in relation to D6

(here reference 244) that '*immunoblots with these antibodies are inconsistent with the presently known structure of the TSHR*'. As concerns the alleged low potency of the mAbs reported in D6, derivable from the statement in the same para. that '*functional effects were observed at extremely high mAb concentrations ...*' the foregoing considerations that the antibodies' potency is not a feature of the claims apply. Finally, the further statement contained in said para. and implicated by the Applicant that '*the use of these mAbs faded from the literature in subsequent years*' does not equate to a lack of enablement, but may equally reflect on the availability of more potent or otherwise more interesting antibodies.

4.7 In conclusion, the ED considers none of D9-D13 to provide evidence that the antibodies disclosed in D4-D6 either do not fall under the claims' scope or that they are not enabled. Moreover, given the broad definition of binding partners covered by claims 1-3 embracing TSHR antibodies which inhibit binding of TSH to TSHR and/or stimulate TSHR, these documents are considered novelty-destroying for claims 1-3.

4.8 D5 discloses an antibody TRMo-2 which in addition to inhibiting TSH also stimulates thyroid adenylate cyclase (Fig. 2 and 3; p. 16344, r-h c. para. 2). Also D6 discloses such an antibody 208F7 (Fig. 1 and 2). The fact that claim 4 requires the said stimulatory and inhibitory activity to be tested differently than done in D5 and D6 does not establish novelty.

4.9 Claims 6-17 and 28-33 refer to stimulatory and/or inhibitory activities as determined in relation to defined quantities of an International Standard. It is however noted that the amount of binding partner tested for these activities is not defined. Thus, any binding partner having either or both properties will meet the respective criteria if tested in sufficient amounts. In other words, these claims are only limiting inasmuch as they require the binding partner to be inhibitory and/or stimulatory, but fail to imply any particular potency. Consequently, said claims lack novelty over D5 and D6 inasmuch as TSHR antibodies displaying both inhibitory and stimulatory properties are concerned and over D4-D6 inasmuch as stimulatory, non-inhibitory TSHR antibodies are concerned as well as over D5 and D6 inasmuch as inhibitory, non-stimulatory TSHR antibodies are concerned.

5 *Inventive step (Art. 56 EPC):*

5.1 As discussed hereinabove the stimulatory and/or inhibitory TSHR antibodies derived from hyperthyroid Graves' patients are known in the art from D4-D6. On the basis of the information provided in these documents the isolation of further such antibodies appears to be a matter of routine even if the screening for antibodies having e.g. both stimulatory and inhibitory properties may be cumbersome. In fact, D13 under section VI provides further guidance how to isolate such antibodies. No information comes forth from the application that the isolation of such antibodies requires technical considerations beyond said routine. In fact, the Applicant in his letter of 28.05.2008, at p.7, para. 3 ac-

knowledges that the generation of such antibodies is a matter of routine. Thus, an inventive step could only be acknowledged if the antibody as such displayed surprising technical properties. The Applicant holds that hMAB TSHR1 would do so. However, none of the claims defines the properties of said antibody in functional or structural terms. As discussed hereinabove the functional parametric definitions do not define a minimum stimulatory and inhibitory potency. As concerns claims defining the antibody in structural terms such a surprising potency associated with hMAB TSHR1 requires a definition of all six CDRs of the heavy and light chain defining the antigen binding site and thus the antibody's specificity. The only claim which achieves this requirement is claim 21. The other claims leave parts of the antigen binding site undefined and thus no technical effect comes forth from these structurally defined antibodies.

5.2 The inventiveness of products related to the said TSHR antibodies, uses thereof and processes of their preparation hinges on the inventiveness of said antibodies. A detailed analysis of claims related to such subject-matter will be performed once the issue of novelty and inventive step of the antibodies has been resolved.

6 D10 and D11 disclose potent stimulatory TSHR antibodies that inhibit the binding of TSH to TSHR. These two documents would be highly relevant to the question of novelty and inventive step if the priority date of 29.11.2002 claimed from 0227964.4 were not valid (Art. 87 and 88 EPC). The Applicant is thus asked to indicate the passages in the said priority document corresponding to the claims on which the subsequent examination is to be based.